APOPTOSIS IS INDUCED BY EXPRESSION OF MUTANT AMYLOID PRECURSOR PROTEIN IN NEURONAL CELLS,
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The identification of several mutations in the amyloid precursor protein (APP) gene of certain familial Alzheimer disease pedigrees suggests that altered APP metabolism underlies the disease mechanism of these individuals. We previously demonstrated that NGF differentiated PC12 cells expressing mutant APPs (APP692, APP693 and APP717F) undergo morphological changes leading to cell death, which is correlated with an increased level of large carboxyl terminal fragments of APP within the cells (Neurobiology of Aging, 15(S1): S56, 1994). We now report evidence of the apoptotic nature of neurodegeneration in these cell lines. DNA from PC12 cells stably transfected with APP constructs exhibited a ladder of oligonucleosome-length fragments characteristic of apoptosis after exposure to NGF and cAMP for 6 days. The intensity of DNA ladders was increased in all mutant APP transfected cell lines as compared to wild-type APP transfected cells. These DNA fragmentation results in both wild-type and mutant APP transfected cell lines were confirmed by *in situ* TUNEL and flow cytometric techniques. The percentage of apoptotic cells increased 6-10 fold in mutant APP, but less than twofold in wild-type APP transfected cells, compared to untransfected cells. Scanning electron microscopic analysis showed extensive soma blebbing in the cells expressing mutant APPs, resulting in a reduction of cell size. Transmission electron microscopic analysis revealed patches of condensed chromatin lying against the nuclear membrane and well-preserved mitochondria and Golgi organelle structures.

These results suggest that mutant APP induced neuronal degeneration occurs via an apoptotic mechanism, which may contribute to the neuronal loss in Alzheimer disease. Our *in vitro* culture system is useful to further study the cellular mechanisms of neurodegeneration induced by mutations of APP and to investigate rational therapeutic strategies.